REMARKS

Amendments to the Claims

Claim 4 has been amended without prejudice and new claims 16 and 17 have been introduced to recite preferred embodiments of applicants' invention that are more clearly differentiated from the prior art and whose metes and bounds are more clear and definite.

Amended claim 4 specifies that the claim is drawn to a method of reducing the effects of neuroendocrine-mediated, psychologically-induced stress on the skin of a human or animal (page 2, lines 1-4).

Claim 4 has also been amended to correct informalities in nomenclature. Specifically, "ginseng RbI" has been replaced with "ginsenoside Rb1" and "ginseng Rc" has been replaced with "ginsenoside Rc" (Page 39, Table 2).

New claim 16 specifies that the composition recited in the method of claim 4 is capable of inhibiting both glucocorticoid-induced chronic stress in a dermal cell and glucocorticoid-induced chronic stress in a cell involved in skin inflammatory responses (page 3, lines 5-9).

New claim 17 specifies that the combination of the first and second substance inhibits glucocorticoid-induced chronic stress in a dermal cell or glucocorticoid-induced chronic stress in a cell involved in skin inflammatory responses as measured by an in vitro assay comprising the following steps:

(i) contacting a dermal cell or a cell involved in skin inflammatory responses with the composition in the presence of a glucocorticoid receptor agonist under conditions and for a period of time that would, in the absence of the candidate first and second substance, lead to the cell being chronically stressed;

(ii) subjecting the cell to acute stress;

(iii) analysing one or more cellular markers selected from a marker of inflammatory cell recruitment, where the cell is a cell involved in skin inflammatory responses; a marker of matrix degradation, where the cell is a dermal cell; and/or a marker of matrix synthesis in the cell, where the cell is a dermal cell;

(iv) determining whether the composition affects the status of the one or more cellular markers;

(v) selecting a composition identified in (iv) as affecting the status of the one or more cellular markers; and

(vi) admixing said compound with a cosmetically or pharmaceutically acceptable carrier or diluent.

Support is provided on page 3, line 23 to page 4, line 5 and in Examples 1 and 2.

Claims Objection

The objection to claims 1 and 3 is rendered moot since these claims have been canceled.

Claim 4 has been amended as suggested by the Examiner to replace "ginseng Rbl" by "ginsenoside Rb1" and "ginseng Rc" by "ginsenoside Rc".

Claims Rejection under 35 USC §101

The rejection of claims 1-3 under 35 USC §101 has been rendered moot since these claims have been cancelled.

Claims Rejection under 35 USC §112

Claims 4-7 were rejected under 35 USC §112, second paragraph as being indefinite. The Examiner asserted that the limitation in the preamble "psychologically-mediated stress on the skin is vague as it is unclear as to the metes and bounds of this limitation.

Claim 4 has been amended to specify that the claims are drawn to a method of of reducing the effects of neuroendocrine-mediated, psychologically-induced stress on the skin of a human or animal.

Applicants disclose on page 1, lines 11-13 that "*Neuroendocrine stress resulting from every day life occurrences has been shown, through longitudinal studies, to be a key driver of age-associated conditions*".

In the summary of the invention (page 1, line 28 to page 2 line 8) applicants further disclose that "*We have also found that chronically stressed skin cells demonstrate a significant increase in sensitivity to acute stress, as demonstrated by an increase in expression of proteins involved in the skin inflammatory response.*

These finding have enabled us to develop an assay method for identifying compounds that are capable of reducing the effects of neuroendrocrine-mediated stress, such as psychologically induced stress, on skin condition. Using this assay we have identified a number of agents that reduce the deleterious effects of chronic glucocorticoid exposure on the ability of skin cells to respond to acute stress".

Applicants respectfully submit that, as the attached article from encyclopedia2.the free dictionary.com demonstrates, the term *neuroendrocrine-mediated, physiologically induced stress* is a well known in psychology and biology in general. The article states in pertinent part (emphasis added):

> "Among the many neurotransmitter systems activated by stress is noradrenaline, produced by neurons with cell bodies in the brainstem that have vast projections up to the forebrain and down the spinal cord. Stressful experiences activate the noradrenergic

system and promote release of noradrenaline; severe stress leads to depletion of noradrenaline in brain areas such as the hypothalamus. ....

Stress also activates the neurally mediated discharge of adrenaline from the adrenal medulla and of hypothalamic hormones that initiate the neuroendocrine cascade, culminating in glucocorticoid release from the adrenal cortex. Thus, the activity of neurons triggered by stressful experiences, physical trauma, fear, or anger leads to hormone secretion that has effects throughout the body. Virtually every organ of the body is affected by stress hormones.... "

In the research article *The physiological effects of psychological stress* (attached), Michael K. Stoskopf teaches in pertinent part (emphasis added) that

".....The interpretation of behavioral observations requires a firm understanding and characterization of the environmental parameters that can induce the physiological state of stress through neurological means in the study subjects. These factors include, but are not limited to, territorial factors, including social and physical accommodations, photo factors, and acoustical factors. Proper interpretation of behavioral observations also requires a

basic understanding of the biochemical and physiological impacts of neuroendocrine-mediated stress...."

Applicants submit that the numerous scholarly references relating to neuroendocrine-mediated psychologically-induced stress, of which the above articles are only the briefest examples, demonstrate that a person of ordinary skill in the art to which the invention pertains would have well understood the subject matter to which amended claim 4 is drawn, namely a method to reduce the effects on the skin of an neuroendocrine-mediated psychologically-induced stress, i.e., stress to skin brought about by chronic release of glucocorticoids from the neuroendocrine system in response to psychological stress.

In view of the above amendments and remarks, applicants respectfully request that the §112, second paragraph rejection be reconsidered and withdrawn.

Claims Rejection under 35 USC §103

Claims 1-7 were rejected under 35USC §103(a) as being unpatentable over Shefer et al (US 2003/0232091 – hereinafter "Shefer"). Applicants respectfully traverse this rejection.

Shefer is directed to a controlled release system useful to stabilize retinol, retinol derivatives, and extracts containing retinol in cosmetic, dermatological, and pharmaceutical compositions. Shefer teaches stabilized retinol in a solid hydrophobic

particle that sustains the release of retinol during the product shelf life and enables a gradual and prolonged release of effective levels of retinol and other cosmetic, dermatological, and pharmaceutical active ingredients into biological surfaces.....The invention further relates to cosmetic, dermatological, and pharmaceutical products comprising stable retinol in a hydrophobic particle that can deliver effective levels of retinol and other cosmetic, dermatological, and pharmaceutical active ingredients to biological surfaces over an extended period of time (Abstract).

Shefer is silent regarding any method even remotely related to reducing the chronic effects of neuroendocrine mediated psychologically-induced stress on the skin. In fact the only reference to "stress" found in the entire document is in reference to the use of specific botanicals namely that "valerian tincture, extracts of melissa and hop [may be used] to cause a sedative effect in case of superexcitation, sleep disturbances, and *stress"* (page 13, [0135]).

Shefer specifically teaches that anti-inflammatory agents can be included in the controlled release system for stabilizing retinol of the present invention to enhance photoprotection benefits, particularly from UVA. Suitable steroidal anti-inflammatories include hydrocortisone (page 8, [0099]).

In contrast, applicants' claim 4 is directed to a method of reducing the effects of neuroendocrine mediated psychologically- induced stress on the skin of a human or animal.

Applicants have found that the administration of a combination of two substances selected from two different groups, one of which is capable of inhibiting glucocorticoid-induced chronic stress in a dermal cell and the other which is capable of inhibiting glucocorticoid-induced chronic stress in a cell involved in skin inflammatory responses is particularly advantageous in reducing the effects of neuroendocrine mediated psychologically-induced stress.

Applicants have identified suitable substances utilizing an in-vitro model to simulate neuroendocrine-mediated, psychologically-induced stress, which is a chronic condition, by repeated application of a glucocorticoid, specifically hydrocortisone, to dermal and endodermal cells.

Based on extensive screening, one substance is selected from the group consisting of ginsenoside Rb1, ginsenoside Rc, curcumin, 22-OH-cholesterol, ciglitazone, mevinolin, commipheric acid, okadaic acid, liquorice extract and mixtures thereof; while the other substance is selected from the group consisting of wolfberry extract, shiitake extract, activin, ginseng Rbl, ginseng Rc, curcumin, ciglitazone with the proviso that the first and second substances must be different.

The Examiner asserted that Shefer teaches a dermatological composition that can comprise gensenoside Rc, circumin, and licorice as active ingredients because Shefer teaches these materials as optional "skin soothing" ingredients at page 9 and 10, [0107]. The Examiner further asserted that it would have been obvious at the time

of the invention to administer this composition to an individual based on its anti-inflammatory properties for skin care.

Just because one could have reconstructed applicants invention by combining various optional or alternative materials disclosed in a reference is no reason to do so. Paragraph 107 of Shefer in fact alphabetically lists over *400* compounds that can be optionally included. However, none of these compounds are used in any of compositions taught in the examples.

Applicants' respectfully submit that it is only through hindsight that the combination of gensenoside Rc, circumin, and licorice could be considered as having been an obvious combination even for the purposes disclosed by Shefer, e.g., to be incorporated into retinol capsules.

Applicants' have not tested all the 400+ compounds listed by Shefer for their ability to inhibit glucocorticoid-induced chronic stress in either a dermal cell or a cell involved in skin inflammatory responses. However, applicants' have tested both rosemary and an extract of pine bark (Pychnogel) which are two compounds that Shefer identifies as suitable skin soothing agents (page 10, [0107]). Both ingredients have been found to be ineffective in inhibiting glucocorticoid-induced chronic stress (Table 2 page 39).

The Examiner asserted that it would have been obvious at the time of the invention to administer a composition to an individual based on its anti-inflammatory properties for skin care. Although this may apply to some types of dermatological preparations, it is certainly not true for compositions to be specifically used in a method of reducing the effects of neuroendocrine-mediated psychologically- induced stress on the skin.

Applicants have demonstrated in Table 2 on page 39 that just because an agent has anti-inflammatory properties does not ensure that it will be effective in inhibiting glucocorticoid-induced chronic stress in either a dermal cell or a cell involved in skin inflammatory responses. For example, applicants have demonstrated that the anti-inflammatory agents Resveratrol and WY14643 are both ineffective in inhibiting glucocorticoid-induced chronic stress (Table 2, page 39).

Finally, as the Examiner has pointed out, Shefer teaches that hydrocortisone is suitable for inclusion in the composition. Applicants respectfully point out that hydrocortisone is the specific glucocorticoid which is used in the current invention to induce chronic stress. Applicants' method of treatment employs compounds which specifically act as glucocorticoid *receptor agonists* and thus the use of hydrocortisone would be counter to the goals of the current invention.

In summary, Shefer is directed to the problem stabilizing retinol in skin care compositions. This is very different from applicants' problem which involves providing a method that can be used by individuals to reduce the effects of neuroendocrine-

mediated, psychologically-induced stress on their skin. Shefer makes no reference to this problem or anything remotely related to it. Applicants respectfully submit that it is only through hindsight using applicants' disclosure as a blueprint, that Shefer could be regarded as having taught that any composition requiring the specific combinations of first and second ingredients be specifically prepared to practice applicants' method recited claim 4.

Claims 16 and 17 are even further removed from Shefer because they recite additional limitations not taught or suggested by Shefer.

Claim 16 specifies that the composition recited in the method of claim 4 is capable of inhibiting both glucocorticoid-induced chronic stress in a dermal cell and glucocorticoid-induced chronic stress in a cell involved in skin inflammatory responses. Shefer is silent reguarding inhibiting glucocorticoid-induced chronic stress, let alone inhibiting it in both a dermal cell and a cell involved in skin inflammatory responses, e.g., endodermal cells.

Claim 17 specifies that the combination of the first and second substance inhibits glucocorticoid-induced chronic stress in a dermal cell or glucocorticoid-induced chronic stress in a cell involved in skin inflammatory responses as measured by a specific in-vitro assay. Shefer is silent regarding glucocorticoid-induced chronic stress and *any* in-vitro assay.

In light of the above amendments and remarks, applicants respectfully request that the §103(a) rejection over Shefer et al be reconsidered and withdrawn.

Claims 1-3 were rejected under 35 U.S.C. § 103(a) as being obvious over Jua-Fei Chen (WO 00/64278). This rejection is rendered moot in view of the cancelling of claims 1-3.

Applicants respectfully request that the application be allowed to issue as a patent.

In the event any questions remain, the Examiner is kindly invited to contact the undersigned agent at her earliest convenience.

Respectfully submitted,

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(computer science)

A problem-oriented programming language used to solve structural engineering problems. Derived from structural engineering system solver.

Stress (psychology)

Generally, environmental events of a challenging sort as well as the body's response to such events. Of particular interest has been the relationship between stress and the body's adaptation to it on the one hand and the body's susceptibility to disease on the other. Both outcomes involve behavioral and brain changes as well as psychosomatic events, that is, changes in body function arising from the ability of the brain to control such function through neural output as well as hormones. One problem is that both environmental events and bodily responses have been referred to interchangeably as stress. It is preferable to refer to the former as the stressor and the latter as the stress response. The stress response consists of a cascade of neural and hormonal events that have short- and long-lasting consequences for brain and body alike. A more serious issue is how an event is determined to be a stressor. One view is to define a stressor as an environmental event causing a negative outcome, such as a disease. Another approach is to view stressors as virtually any challenge to homeostasis and to regard disease processes as a failure of the normal operation of adapative mechanisms, which are part of the stress response. With either view, it is necessary to include psychological stressors, such as fear, that contain implied threats to homeostasis and that evoke psychosomatic reactions. These are reactions that involve changes in neural and hormonal output caused by psychological stress. Psychosomatic reactions may lead to adaptive responses, or they may exacerbate disease processes. Whether the emphasis is on adaptation or disease, it is essential to understand the processes in the brain that are activated by stressors and that influence functions in the body. *See* Homeostasis, Psychosomatic disorders

Among the many neurotransmitter systems activated by stress is noradrenaline, produced by neurons with cell bodies in the brainstem that have vast projections up to the forebrain and down the spinal cord. Stressful experiences activate the noradrenergic system and promote release of noradrenaline; severe stress leads to depletion of noradrenaline in brain areas such as the hypothalamus. This release and depletion of noradrenaline stores results in changes at two levels of neuronal function: phosphorylation is triggered by the second-messenger cyclic AMP and occurs in the presynaptic and postsynaptic sites where noradrenaline is released and where it also acts; synthesis of new protein is induced via actions on the genome. Both processes enhance the ability of the brain to form noradrenaline when the organism is once again confronted with a stressful situation. Other neurotransmitter systems may also show similar adaptive changes in response to stressors. *See* Noradrenergic system

Stress also activates the neurally mediated discharge of adrenaline from the adrenal medulla and of hypothalamic hormones that initiate the neuroendocrine cascade, culminating in glucocorticoid release from the adrenal cortex. Thus, the activity of neurons triggered by stressful experiences, physical trauma, fear, or anger leads to hormone secretion that has effects throughout the body. Virtually every organ of the body is affected by stress hormones. The hypothalamic hormone (corticotrophin-releasing hormone) that triggers the neuroendocrine cascade directly stimulates the pituitary to secrete ACTH. In response to certain stressors, the hypothalamus also secretes vasopressin and oxytocin, which act synergistically with corticotrophin-releasing hormone on the pituitary to potentiate the secretion of ACTH. Various stressors differ in their ability to promote output of vasopressin and oxytocin, but all stressors stimulate release of corticotrophin-releasing hormone. Other hormones involved in the stress response include prolactin and thyroid hormone; the metabolic hormones insulin, epinephrine, and glucagon; and the endogenous opiates endorphin and enkephalin. *See* Endorphins

Of all the hormones in the endocrine cascade initiated by stress, the glucocorticoids are the most important because of their widespread effects throughout the body and in the brain. The brain contains target cells for adrenal glucocorticoids secreted in stress, and receptors in these cells are proteins that interact with the genome to affect expression of genetic information. Thus, the impact of stress-induced activation of the endocrine cascade that culminates in glucocorticoid release is the feedback of glucocorticoids on target brain cells. The effect is to alter the structure and function of the brain cells over a period of time ranging from hours to days.

In the case of noradrenaline, glucocorticoids have several types of feedback effects that modify how the noradrenergic system responds to stress. Glucocorticoids inhibit noradrenaline release, and they reduce the second-messenger response of brain structures such as the cerebral cortex to noradrenaline. Glucocorticoid feedback also affects the serotonin system, facilitating serotonin formation during stress but at the same time altering the levels of several types of serotonin receptors in different brain regions, which has the net effect of shifting the balance within the serotonergic system. Taken together, evidence points to a role of glucocorticoid secretion in leading to restoration of homeostatic balance by counteracting the acute neural events such as increased activity of noradrenaline and serotonin, which are turned on by stressful experiences. Other neurotransmitter systems may also respond to glucocorticoid action. Moreover, the other hormones activated by stress have effects on the brain and body that must be considered. *See* Serotonin

In general, stress hormones are protective and adaptive in the immediate aftermath of stress, and the organism is more vulnerable to many conditions without them. However, the same hormones can promote damage and accelerate pathophysiological changes, such as bone mineral loss, obesity, and cognitive impairment, when they are overproduced or not turned off. This wear-and-tear on the body has been called allostatic load. It is based upon the notion that allostasis is the active process of maintaining stability, or homeostasis, through change, and allostatic load is the almost inevitable cost to the body of doing so.

Stress hormone actions have important effects outside the brain on such systems as the immune response. Glucocorticoids and catecholamines from sympathetic nerves and the adrenal medulla

participate in the mobilization and enhancement of immune function in the aftermath of acute stress. These effects improve the body's defense against pathogens but can exacerbate autoimmune reactions. When they are secreted chronically, the stress-related hormones are generally immunosuppressive; such effects can be beneficial in the case of an autoimmune disease but may compromise defense against a virus or bacterial infections. At the same time, glucocorticoids are important agents for containing the acute-phase response to an infection or autoimmune disturbance. In the absence of such containment, the organism may die because of the excessive inflammatory response. *See* Immunology

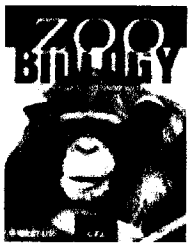
Besides affecting the immune response, stressors are believed to exacerbate endogenous depressive illness in susceptible individuals. Major depressive illness frequently results in elevated levels of cortisol in the blood. It is not clear whether the elevated cortisol is a cause or strictly a result of the brain changes involved in depressive illness. *See* Affective disorders

STRESS - STRuctual Engineering Systems Solver.

A system for structural analysis problems in Civil Engineering. STRESS was superseded by STRUDL.

["STRESS: A User's Manual", S.J. Fenves et al, MIT Press 1964].

[Sammet 1969, p. 612].



Zoo Biology

Volume 2 Issue 3, Pages 179 - 190

Published Online: 16 May 2005

Research Article

The physiological effects of psychological stress

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KEYWORDS

stress • territory • light • sound • xenobiotic • immunology

ABSTRACT

The study of behavior is a powerful tool in the captive management of wild animals. It can, if properly applied, provide insight into a wide variety of problems. The interpretation of behavioral observations requires a firm understanding and characterization of the environmental parameters that can induce the physiological state of stress through neurological means in the study subjects. These factors include, but are not limited to, territorial factors, including social and physical accommodations, photo factors, and acoustical factors. Proper interpretation of behavioral observations also requires a basic understanding of the biochemical and physiological impacts of neuroendocrine-mediated stress. These include alterations in an individual's ability to metabolize toxic substances, resist infections, and reproduce. Confounding effects of these alterations must be considered in the examination of behavioral data. The most powerful experimental designs in comparative behavior are those that concurrently examine environmental stressors, physiological status, and behavior.

Received: 10 October 1982; Accepted: 19 February 1983

DIGITAL OBJECT IDENTIFIER (DOI)

10.1002/zoo.1430020304 About DOI